REMARKS

Status of the Claims

Claims 1 and 80-84 are currently pending in the application.

Claims 1 and 80-84 remain under consideration with entry of this Response.

Summary

On 16 March 2010 applicants submitted a Supplemental Response to the Office Action dated 25 June 2009. On 17 March 2010, the Office mailed a new, non-final Office Action. Applicants' 16 March 2010 Response and the 17 March 2010 Office Action crossed in the mail. On 17 June 2010, the Office entered applicants' Supplemental Response into the record and concurrently issued a new, final Office Action (dated 17 June 2010), expressly vacating the Office Action dated 17 March 2010. Accordingly, the status of the claims is as follows: **(a)** claim 80 stands rejected under 35 U.S.C. §112, first paragraph, on the basis of written description; and **(b)** claims 1 and 80-84 stand rejected under 35 U.S.C. §103(a) as unpatentable over Tipton. Applicants respectfully traverse all pending claim rejections for the following reasons.

The Rejection under 35 U.S.C. §112, First Paragraph

Claim 80 stands rejected under 35 U.S.C. §112, first paragraph, on the basis of written description. In particular, the Office asserts that the recitation that the network former is present at 1-8.6 wt% "was not envisioned at the time the application was filed." Office Action at page 3. In response, applicants direct the Office's attention to the published specification (US 2004/0161382), at Paragraph [0075], the second line of the second column appearing at page 7 where it is stated that the network former is present "from about 1% to about 8.6%." Reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is thus respectfully requested.

The Rejection under 35 U.S.C. §103(a)

Claims 1 and 80-84 stand rejected under 35 U.S.C. §103(a) as unpatentable over Tipton. In particular, the Office continues to assert that Tipton discloses a composition on the basis that elements from applicants' recited combination can be found in various excipient lists from Tipton. Applicants respectfully traverse the rejection for the following reasons.

Initially, applicants note that the Office has created an entirely circular argument that begins and ends with an improper assumption. In this regard, the Office has used the Tipton reference as a catalogue of separate parts, combining multiple, distinct teachings from Tipton to arrive at an artificial combination of unconnected elements which is then declared "the composition" of Tipton. The Office then turns the full circle by comparing this artificial combination ("the composition" of Tipton) to applicants' recited invention, and asserting that "the composition" of Tipton would be expected to have the same properties as applicants' composition.

Applicants have disclosed and claimed compositions having the unique and beneficial characteristics of providing for robust, long term delivery (e.g., between 1-20 hours or greater) of potent and potentially dangerous drugs when the compositions are taken as intended, while at the same time the subject formulations are also able to resist unwanted extraction of the entire drug dose as a result of simple extraction techniques such as those that can be performed using the commonly accessible solvent ethanol. These beneficial characteristics are expressly recited in claims 1 and 80-84. Applicants further disclosed in their specification that a composition having such mutually exclusive characteristics represent a surprising result. Applicants carried out a series of experiments showing that their compositions have both of these beneficial, recited characteristics and reported these studies in their working examples. The Office asserts that "applicants have not provided a factual showing to show what is unexpected over the prior art". Office Action at pages 8-9. This assertion is clearly incorrect. Applicants have expressly disclosed their unexpected results and provided working examples to demonstrate those unexpected results. This express, factual showing is clearly not "attorney arguments taking the place of evidence in the record" as the Office asserts

(Office Action at page 9). If the Office believes that applicants' factual showing of their recited characteristics is somehow in error, the Office bears the burden to establish why those expressly reported data are incorrect or inaccurate. In addition, since the Office seems to be taking a contrary position to applicants' (not applicants' attorney) express disclosure of unexpected results, the Office bears the burden to establish why applicants are incorrect.

At pages 9-10 of the Office Action, the Office asserts that applicants' disclosure at Paragraphs [0018], [0080], [0082], [0084], [0116]-[0119], [0132]-[0135], [0013], [0014] and [0015], where applicants discuss their recited unexpected results, is not relevant since the studies were carried out with a formulation containing SAIB:ethyl lactate:IPM:CAB and with oxcodone formulations, that "do not represent the claimed formulation". Applicants are, with all due respect, unsure how to respond to such an assertion. The claims that are under examination are limited to compositions containing SAIB, ethyl lactate as a solvent (see the Requirement for Election of Species dated 12 February 2007), oxycodone as a drug (see the Requirement for Election of Species dated 12 February 2007), a network former that includes CAB (see entire specification and pending claim 81), and a rheology modifier that includes IPM (see entire specification). In other words, the working examples that show applicants' unexpected results were carried out with the same formulations that are currently under examination. In light of this apparent confusion, applicants respectfully request that the Office clarify its' position that the experimental data presented in applicants' working examples was generated using a different formulation from those recited in claims 1 and 80-84.

The proper analysis under Section 103 must look at applicants' claimed combination, with its expressly recited characteristics, and then demonstrated that Tipton somehow enabled that particular combination to the skilled person, pointing to specific technical rationale available from Tipton or existing in the prior art to make that particular combination. The Office has failed to make this proper analysis. The Office has failed to provide a rational basis why one would want or need to combine certain specific elements from Tipton, picking and choosing among the various part catalogs, to somehow arrive at applicants' recited invention. In fact, the Office has had to skip from

Tipton's general disclosure of controlled release compositions found in columns 7 – 10, to an unrelated and distinct specific disclosure of a mouthwash composition found in columns 11 and 12, and then skip to claim 88 just in order to find a sufficient number of individual elements to form the core of applicants' claimed combination. Given the differences between these various sections of the Tipton reference, applicants strongly contest the Office's position that such picking and choosing was obvious in light of Tipton (that is, applicants' recited invention as a whole was an obvious modification of the Tipton disclosure and that the skilled person would have recognized this particular combination and had a reasonable expectation for success for that combination), when there is simply no technical basis for this assertion. The sole basis that the Office has provided to support its piecemeal, hindsight reconstruction of applicants' specific combination is that Tipton teaches that additives can be added to pharmaceutical compositions as desired to modify the properties, and that Tipton did not expressly forbid combining applicants' recited elements.

Applicants respectfully submit that this line of reasoning is technically incorrect and fails to meet the minimum standard for obviousness. More particularly, applicants have disclosed and claimed a particular set of pharmaceutical excipients that are combined to provide an oral, controlled release pharmaceutical formulation suitable to provide for long term delivery (e.g., between 1-20 hours or greater) of potent and potentially dangerous drugs, where the subject formulations are also able to resist unwanted extraction of the entire drug dose as a result of simple extraction techniques such as those that can be performed using the commonly accessible solvent ethanol. These twin required performance characteristics of applicants' formulations are diametrically opposed requirements, where the skilled person understood that developing a composition having one feature (e.g., provide long term controlled delivery) would be expected to eliminate the other feature (e.g., resist extraction into ethanol), and *vice-versa*. Accordingly, applicants' recited formulations provide unexpected and surprising results.

Initially, applicants submit that the Office has failed to provide persuasive reasoning (i.e., some sort of articulated reasoning with rational underpinning to support

the legal conclusion of obviousness) to start with any of the compositions actually described by Tipton and then modify that starting composition to form applicants' expressly recited combination. Failure to provide such persuasive reasoning has consistently been found to support a finding of non-obviousness by the Federal Circuit applying the KSR standards for obviousness (*KSR Intern. Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007)). See, e.g., *Takeda Chem. Indus, Ltd. V. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007) (where the court found that, rather than identifying a predictable solution, the prior art disclosed a broad selection of compounds any of which could be selected for further investigation, and further that there was nothing in the prior art to narrow the possibilities, nor anything to suggest making the modifications that were necessary to arrive at the claimed compositions); *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008) (where the court found that one of ordinary skill in the art would not have any reason to select among several unpredictable alternatives to produce the invention, and that, without any clue of potential utility of the claimed composition, one would have no reason to develop that composition in the first place – the court also noted that evidence of objective criteria showing non-obviousness, including unexpected results, were of particular importance); *Eisai Co., Ltd. V. Dr. Reddy's Labs, Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008) (where the court found that a *prima facie* case of obviousness for a chemical compound begins with a reasoned identification of a lead compound, and that the record contained no reasons why the skilled artisan would have considered modification of a lead compound as an identifiable, predictable solution); and *Proctor & Gamble v. Teva Pharm.*, 566 F.3d 989 (Fed. Cir. 2009) (where the court found that one must determine whether, at the time of the invention, a person having ordinary skill would have had reason to attempt to make the claimed composition and a reasonable expectation of success in doing so, and that, to the extent an art is unpredictable, as the chemical arts often are, *KSR's* focus on 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable, citing *Eisai, Id.*, and *KSR*). In fact, the Supreme Court itself has noted that it will often be necessary "to determine whether there was an apparent reason

to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).

Applicants' recited compositions, having their recited unexpected and surprising characteristics, cannot qualify as "identified, predictable solutions," that enjoy a reasonable expectation of success. Something that is unexpected and surprising cannot also be predictable and expected. The sort of apparent / persuasive reasoning required to support a showing of obviousness is not a simple matter of listing prior art, asserting some generalized motivation "to modify properties" with "additives", and then concluding with the stock phrase "therefore, to one skilled in the art it, would have been obvious to perform the claimed invention". Rather, there must be some apparent and rational basis for connecting unrelated disclosure from Tipton to produce applicants' specific, recited pharmaceutical formulation combinations, particularly in light of the unexpected and surprising performance features of those formulations. A mere generalized desire "to modify" chemical properties in a pharmaceutical product by "using additives" is simply not enough under a proper KSR analysis of obviousness in the chemical arts. See, e.g., *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363 (Fed. Cir. 2008). Accordingly, the rejection of the claims as obvious over Tipton is improper.

In addition, applicants submit that a proper consideration of secondary considerations under a Graham Factor analysis provides further support for a conclusion of non-obviousness over Tipton. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, (1966). As noted by the Federal Circuit, the presence of secondary considerations such as long-felt but unsolved need, failure of others and unexpected results "may often be the most probative and cogent evidence [of non-obviousness] in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Post KSR, the Federal Circuit has confirmed the strength of such considerations, noting that evidence of objective criteria showing non-obviousness, including unexpected results, is of "particular importance". *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358 (Fed. Cir. 2008).

Applicants' recited combination exhibits unexpected and surprising results in providing an oral dosage form that serves demonstrates both favorable drug release

kinetics when ingested as intended, but also resists drug extraction for the dosage form when under a condition of abuse such as extraction into ethanol. These unexpected and surprising results are expressly recited in the claims and are clearly described by applicants, for example at Paragraph [0018], applicants state:

"A particular advantage of [the invention is] it provides an oral dosage form comprising a formulation ... effective to reduce the rate of extraction of the drug, for example with water, ethanol, or other solvents, while simultaneously providing desired drug release kinetics."

Also, at Paragraph [0080], applicants state:

"The current invention also disclosed new and surprising interrelationships between the formulation ingredients, which resulted in unique and non-obvious formulation rheology, drug release kinetics, rate and extent of drug adsorption in vivo, and/or desirable abuse deterrence characteristics including reduced drug extractability, for example, by alcoholic or aqueous solutions."

Furthermore, at Paragraph [0082] applicants state:

"The dosage forms of the invention show unexpectedly favorable drug-release kinetics" and at Paragraph [0084], applicants state "the drug-release kinetics ... can be seen to be both unexpected and favorable for delivery of drugs such as oxycodone."

In addition, applicants demonstrate dosage forms having these combined properties in their working examples. See Paragraphs [0116 – 0119] and [0132 – 0135] and Figures 5 and 7 for drug release performance; and Paragraphs [0120 – 0129] and Figures 1-4 and 11 for extraction of drug into ethanol. These unexpected and surprising results are strong indicia of non-obviousness (in KSR, the Supreme Court, affirming *United States v. Adams*, held that the fact that elements worked together in an unexpected and fruitful manner supported the conclusion that *Adam's* design was not obvious to those skilled in the art). *KSR, Id.*

Applicants' invention also answers a long-felt but unsolved need in the pharmaceutical arts. This unsolved need was discussed by applicants, for example at Paragraph [0005], where applicants state:

"Another challenge is to produce a dosage form ... that reduces the potential for drug abuse. In particular, opioids, CNS-depressants, and stimulants are commonly abused. According to a 1999 study by the National Institute on Drug Abuse (NIDA), and estimated 4 million people ... were (at the time of the study) using prescription drugs "non-medically." Of these, 2.6 million misused pain relievers, 1.3 million misused sedatives and tranquilizers, and 0.9 million misused stimulants."

At Paragraph [0013], applicants state:

"Solid dosage forms are particularly susceptible to abuse ... [a]ddicts ... grind the tablet to extract the drug into alcohol or water to make a concentrated injectable drug solution ... [t]hese well-known techniques for drug abuse have been used for many years with all manner of drugs."

At Paragraph [0014], applicants state:

"One particularly important example of a highly addictive drug that is commonly abused by ... alcohol and/or water extraction ... is Oxycodone ... [i]t has been alleged that Oxycontin® abuse has so far resulted in at least 120 deaths nationwide ... [o]verdose produces small pupils, slow breathing, dizziness, weakness, seizures, the loss of consciousness, coma, and sometimes death."

Then, at Paragraph [0015], applicants note:

"The above problems present a clear and long-felt challenge to drug manufacturers to produce drug dosage forms that also allow for desirable drug release kinetics and reduced potential for abuse."

Applicants submit that these clear public health and safety concerns have been at the forefront of public press for numerous years, have significantly increased in their magnitude on a yearly basis since the 1999 study described by applicants, and in fact were clearly urgent, yet completely un-met needs facing the drug industry prior to applicants' innovation to produce dosage forms that provide for both excellent controlled release kinetics when administered as intended, and strong resistance to extraction of the drug when subjected to common methods of abuse, importantly extraction of the drug into ethanol (alcohol).

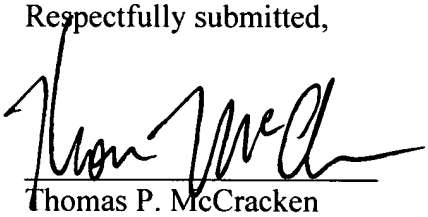
Accordingly, applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness over Tipton. The Office has failed to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make the specific composition recited in applicants' claims, having applicants' unique performance characteristics, and would have had a reasonable expectation of success in doing so. Accordingly, applicants respectfully submit claims 1 and 80 – 84 are patentable over Tipton. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is thus earnestly solicited.

CONCLUSION

Applicants submit that the pending claims define an invention that is both novel and nonobvious over the cited art, and thus all claims are in condition for allowance. Acknowledgement of this by the Office in the form of an early allowance is thus respectfully requested. In addition, if the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicants invite the Examiner to contact the undersigned at (408) 777-4915.

No additional fee is deemed necessary with submission of this Paper. However, if the Commissioner determines that an additional fee is necessary, the Commissioner is hereby authorized to charge any additional fees associated with this communication to Deposit Account No. **50-1953.**

Respectfully submitted,



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